Intern. J. Neuroscience, 2001, Vol. 106, pp. 169–184
Reprints available directly from the publisher
Photocopying permitted by license only

© 2001 OPA (Overseas Publishers Association) N.V.
Published by license under
the Gordon and Breach Science
Publishers imprint.
Printed in Malaysia.

SYNCHRONIZED FEEDING AS A "CONDITIONED STIMULUS" FOR OVERT SEIZURES IN CHRONICALLY (LIMBIC) EPILEPTIC RATS: A MODEL FOR "PSYCHOGENIC SEIZURES" WITH COMPLEX PARTIAL EPILEPSY*

M. A. PERSINGER† and G. CHELLEW-BELLANGER

Behavioral Neuroscience Laboratory, Laurentian University

(Received in final form 24 April 2000)

Chronic limbic epilepsy was induced in male albino rats by a single systemic injection of lithium (3 mEq/kg) and pilocarpine (30 mg/kg). During the subsequent months the numbers of spontaneous, paroxysmal stereotyped episodes (analogous to Racine stages 4 and 5) were monitored. The numbers of these "overt seizures" increased within 10 min of the daily presentation of a food stimulus even though food was available *ad libitum*. The majority of the paroxysmal, stereotyped behaviours occurred within 1 min of the stimulus presentation; they were attenuated by oral prednisolone. Three rats displayed evidence of "conditioned seizures" to specific stimuli. The results suggest that the display of these behaviours can be synchronized and learned in contexts that are associated with the release of CRF (corticotrophin releasing factor) and may involve the disinhibited activity within the central amygdaloid nucleus of these rats. Implications for the occurrence of psychogenic seizures in patients with complex partial (limbic) epilepsy are discussed.

Keywords: Limbic seizure; Complex partial seizure; Conditioning lithium; Pilocarpine; Rat; Food synchronization; Corticotrophin

*Part of this research was supported by a grant from the Laurentian University Research Fund.

†Address for correspondence: Behavioral Neuroscience Laboratory, Laurentian University, Sudbury, Ontario P3E 2C6. Fax: (705)-675-4889, e-mail: MPersinger@admin.laurentian.ca

Copyright ©2001. All Rights Reserved.

INTRODUCTION

Psychogenic seizures are surprisingly common (Porter, 1993) and are frequently displayed by a major subpopulation of patients who exhibit the non-epileptic syndrome (Gates and Erdahl, 1993). Psychogenic seizures do not occur only in patients who do not exhibit EEG-verifiable epilepsy. Approximately one-third (30%) of patients who displayed "pseudoseizures" or psychogenic seizures also exhibited interictal evidence of associated epilepsy (Ramsay, Cohen and Brown, 1993). The etiology of these seizures may reflect a third factor from which both epileptic and non-epileptic seizures emerge (Persinger, 1994). This paper reports a potential experimental (rat) model by which "psychogenic" or learned seizures could be studied.

Psychogenic, non-epileptic patients (whose paroxysmal behaviours have been labelled with the more pejorative descriptors of "hysterical seizures" or "pseudoseizures"), exhibit abnormally elevated emotional conflicts (Mulder, 1990) as inferred by standardized, psychometric testing and display the type of psychological or psychiatric co-morbidity that accompanies elevations of CRF (corticotrophin releasing factor), including depression (Curtis and Valentino, 1994; Weiss, Stout, Aaron, Quan, Owens, Butler and Nemeroff, 1994). This neuropeptide may contribute to the development of psychogenic seizures because of: (1) its capacity to increase spontaneous discharge frequency and to decrease postburst hyperpolarization in hippocampal neurons (Aldenhoff, Gruol, Rivier, Vale and Siggins, 1983) and (2) its direct involvement with the limbic pathways that mediate learning, meaning and stress (Koob, Heinrichs, Menzaghi, Pich and Britton, 1994).

We (Persinger, Makarec and Bradley, 1988; Persinger, Bureau, Kostakos, Peredery and Falter, 1993) have modified a treatment first reported by Honchar, Olney and Sherman (1983) that results in chronic limbic epilepsy. After "recovery" from the initial treatment, these rats exhibit extremely conspicuous automatisms that are very similar or identical to those displayed during verifiable electrical seizures (Racine, 1972). Our continuous video monitoring (between one month to about six months after the initial seizure induction) indicated that spontaneous rearing, forelimb clonus and falling continued to occur about once per day for each rat.

Copyright ©2001. All Rights Reserved.

These "spontaneous" paroxysmal, stereotyped sequences begin with immobility and staring. Head nods are quickly (within 10 sec) followed by (primarily) left forelimb clonus that (within 1 sec) generalizes bilaterally to rapid forelimb clonus. The rat rears and then (usually) falls backwards. About 10% of the episodes generalize to clonic-tonic convulsions. If the latter does not occur, a marked startle response emerges about 30 sec later. The concomitant fear-like facial displays are associated with a pattern of running and jumping similar to the effects of picrotoxin. Most rats return to their preseizure behavior within about 5 min.

Casual observation indicated that the incidence of the spontaneous display of these conspicuous stereotyped behaviours could be modified by pairing the stimulation associated with removal from the cage with conditions that encourage the release of CRF (*e.g.*, intermittent, daily restraint for removal of tail blood or synchronized or daily feeding; Haas and George, 1988). For example, rats housed in groups (3/cage) and fed within 30 min of the same time each day exhibited progressive increases in the proportion of stereotyped events (rearing, rapid forelimb clonus and falling) that simulated a learning curve (Persinger *et al.*, 1993). Similarly, the "temporal evolution" of spontaneous seizures was noted during daily training of these chronic epileptic rats within a radial maze (Harrigan, Peredery and Persinger, 1991).

During the early evening (in the rat) a few hours before the active period there is a two fold increase of CRH41 in the hypothalamus and median eminence, an approximately 3.5 fold increase in plasma ACTH (Ixart, Siaud, Barbanel, Mekaouche, Givalois and Assenmacher, 1993) and a slow rise in circulating corticosterone. Because daily feeding at the same time can be a zeitgeber for elevations in CRF and circulating glucocorticoids (Mistleberger and Rusak, 1988), we reasoned that synchronous presentation of food to these chronic epileptic rats (even when food was available *ad libitum*), would increase release of CRF and increase the probability of overt displays of seizures. If CRF-sensitized neurons within the amygdala were primarily involved, then most of the spontaneous seizures would occur within one minute (several minutes before the expected humoral elevations in either ACTH or corticosterone).

Both our rat (Persinger, 1995) and human (Persinger, 1994) research have implicated the role of the epileptogenic neuropeptide

Copyright ©2001. All Rights Reserved.

corticotrophin releasing factor (CRF) as a promoter of the electrical seizures that generalize to overt (motor) events or to absences. The central nucleus of the amygdala (LeDoux, 1994), which has been associated with the modulation of CRF influence upon the paraventricular hypothalamus (Dallman, Akana, Bradbury, Strack, Hanson and Scribner, 1994) and pituitary, appears to be permanently disinhibited by the initial seizure-induced damage within other amygdaloid nuclei (Bureau, Peredery and Persinger, 1994; Desjardins and Persinger, 1995) that occurs primarily during the first 24 hr after the lithium/pilocarpine injection.

Although "physically" these rats appear normal within about two weeks after the induction of the seizure by lithium/pilocarpine, they frequently display rapid "micromovements" of the pinna and an enhanced acoustic startle reflex within the home cage (Bedard and Persinger, 1995). The suppression of the acoustic startle reflex in response to infusion of CRF after lesions of the central nucleus of the amygdala but not following lesions of the paraventricular nucleus (Liang, Melia, Campeau, Falls, Miserendino and Davis, 1992) or after the oral consumption of the glucocorticoid receptor blocker, predinsolone, is consistent with our hypothesis that transient elevations of CRF enhance the electrical lability conducive to partial seizure behavior while inhibitors dampen this condition.

This experiment was designed to determine if the incidence of paroxysmal, stereotyped overt behaviours (identical to those associated with verifiable, electrical seizures) in the chronic (limbic) epileptic rat could be learned or "synchronized" by manipulation of the rat's environment. The following predictions were consistent with our proposed mechanism: (1) the proportion of rats within the (sample) population that display rapid forelimb clonus and transient incapacitation within 10 min of the daily presentation of a "conditioned" stimulus (food) should increase over time; the cumulative record of these "overt seizures" should reflect an acquisition curve, (2) the frequency of these "overt seizures" should be attenuated during periods when compounds known to reduce CRF release or its effectiveness are administered, (3) most of the paroxysmal stereotyped motor behaviours should occur within about 1 min of the presentation of the food once the daily synchronization has occurred, and (4) the strength of the association between the presentation of food and the

Copyright ©2001. All Rights Reserved.

biochemical changes that evoke the overt seizures should be sufficient, in some rats, for the sound of food presentation (but not related auditory stimuli) to elicit the seizures.

MATERIALS AND METHODS

Seventy-two (72) male Wistar rats obtained from Charles River Breeding (Quebec) served as subjects. All rats were between 80 and 90 days of age at the time they were injected with 3 mEq/kg of lithium chloride and then 4 hr later by 30 mg/kg of pilocarpine. Within 1 hr (about 30 min) after the display of overt forelimb clonus, 25 mg/kg of acepromazine (Atravet, Ayerst Laboratories, Montreal, Quebec) had been injected s.c. in order to promote survival.

After approval by the local animal care committee, the experiments began about two months after the injection of the lithium-pilocarpine. For Experiments I ($n = 32$) and II ($n = 32$) rats were housed in either single wire or plastic cages while in Experiment III (two replications, $n = 8$) rats were housed together ($n = 4$) in a single long cage (Bedard and Persinger, 1995). All rats were maintained within temperature controlled (19 to 21 deg C) rooms. The light : dark cycle was 12 : 12 with the night cycle beginning at 20 : 00 hr.

Food (Purina rat chow) and water were available *ad libitum* for all experiments. Between 19 : 15 and 19 : 30 hr each day two cubes (5 gm each) of rat chow were added to the cages for all of the rats in Experiment I and to only one rack (experimental group, $n = 16$) of the rats in Experiment II (total time required to add food to each rack < 1 min). Two additional groups (8/group) were housed in one of two racks (total $n = 16$) each of which were maintained in different rooms from each other and the experimental group. These two reference groups (food and water *ad libitum*) did not receive any synchronized, daily presentation of food by the experimenters. The two reference groups were employed to minimize the potential effects of simply entering the room at more or less the same time each day and to serve as controls for any intrinsic circadian contribution to the incidence of seizures.

The occurrence of limbic overt seizures, defined by the rapid forelimb clonus, rearing and falling, within the first 10 min after

Copyright ©2001. All Rights Reserved.

introduction of two cubes of food, was recorded. These abnormal sequences are extremely obvious and cannot be confused with normal behaviours such as grooming. Because the central nucleus of the amygdala is critical for mediating the startle reflex, we were careful to enter the rooms quietly and slowly and to generate minimum sounds. The entry into the other two rooms (only one/day) that contained the reference groups was determined randomly by flipping a coin. Although these groups never received the food stimulus, the observer sat at the same distance from the cage. Daily observations were completed for six months for Experiment I and for 13 weeks for Experiment II.

The latency of the delivery of the two food cubes was delayed in Experiment III. The food stimulus was introduced into the cage 10 min after the experimenter entered the room. During two, two week intervals after the numbers of "overt seizures" per week had stabilized, the group continuously received 0.5 mg/cc of prednisolone in the water supply. This dosage had been shown to attenuate the intermale aggression that emerges approximately 20 days after the induction of the chronic epileptic condition (Bedard and Persinger, 1995).

The latencies of onset of the 52 overt seizures displayed by the group over a 3 month period (Experiment I) and of the 60 total overt seizures displayed over 3.5 months (Experiment II) were coded into successive minutes, *i.e.*, occurring between 0 and 1 min, between 1 min 1 sec and 2 min, *etc.* Chi-squared analyses were completed, assuming an equal expected frequency for each of the 10 min. All rats, except for those in the reference group, displayed at least two episodes of paroxysmal behaviours following the food presentation. Statistical analysis involved SPSS software on a Vax 4000 computer.

Three of the seized rats, all of whom required mush (rat chow dissolved in water) intermittently during a four month period, exhibited responses within 30 sec of the daily presentation of food on at least five consecutive days. Each of these rats was removed on separate days and tested in another room during the last hour of the light cycle. During a single 20 min period, each rat was videotaped while sitting in an area 30 cm by 30 cm. One side was opened so the activity could be videotaped. Either the sound of food rattling in a wire cage (the exact sound of dropping food into the cage), the sound of 8 keys on a key ring, or clapping hands, were presented from a

Copyright ©2001. All Rights Reserved.

distance of 1 m for 10 sec each once every approximately 2 min. The sound levels for all three stimuli were comparable (about 70 db) near the position of the rat. There were 3 presentations of food sounds, 3 presentations of key sounds and 3 presentations of clapping. The duration of repeated rearing and rapid forelimb clonus was measured after each presentation.

RESULTS

Chi-squared analyses (Experiment I) for the distributions of the display of spontaneous seizures during the first 10 min after the presentation of the synchronized food stimulus was not random [chi-squared $(df=9)=88.39$, $p<.01$]. As can be seen in Figure 1, 51% of the full displays of rearing and forepaw clonus occurred within one minute of the presentation of the food stimuli (observational estimation from daily notes indicated that at least 20% of seizures occurred within 10 sec of entry into the room).

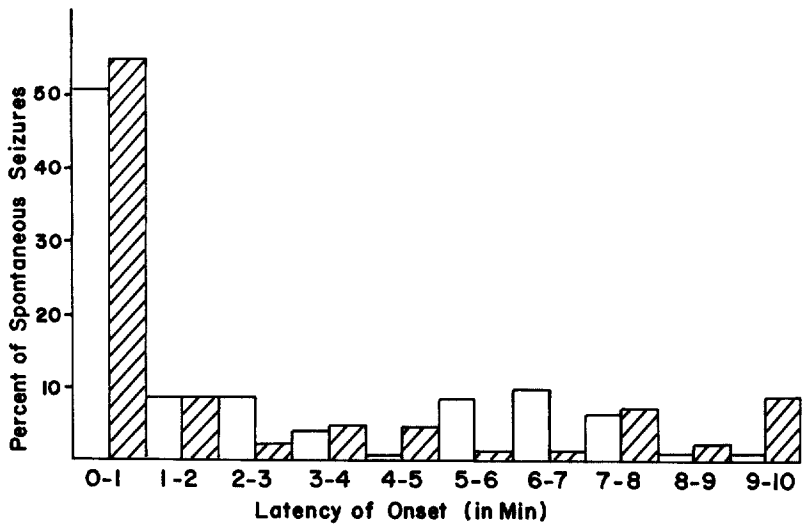

FIGURE 1 Proportion of paroxysmal, stereotyped behaviours (overt seizures) displayed per 1 min interval during the first 10 min after presentation of the (food) stimulus in chronic epileptic rats (Experiment I: open blocks; Experiment II: diagonal lines).

Copyright ©2001. All Rights Reserved.

The cumulative numbers of "overt seizures" per week for the rats that received the daily food stimulus in Experiment II are shown in Figure 2. There was no display of "overt seizures" during the 10 min, post stimulus observation period until about 3 weeks after the daily presentations had begun. The inflection point occurred after about 5 wk. In comparison, the reference groups displayed a total of 8 seizures during this period.

The distribution of the overt paroxysmal displays during the successive 1 min intervals of the 10 min observation period for the rats that received the daily food presentations (Experiment II) is also shown in Figure 1. Chi-squared analysis demonstrated a significant deviation (Chi-squared = 92.01, $p < .001$) from chance expectancy that was due to the greater proportion of overt seizures occurring during

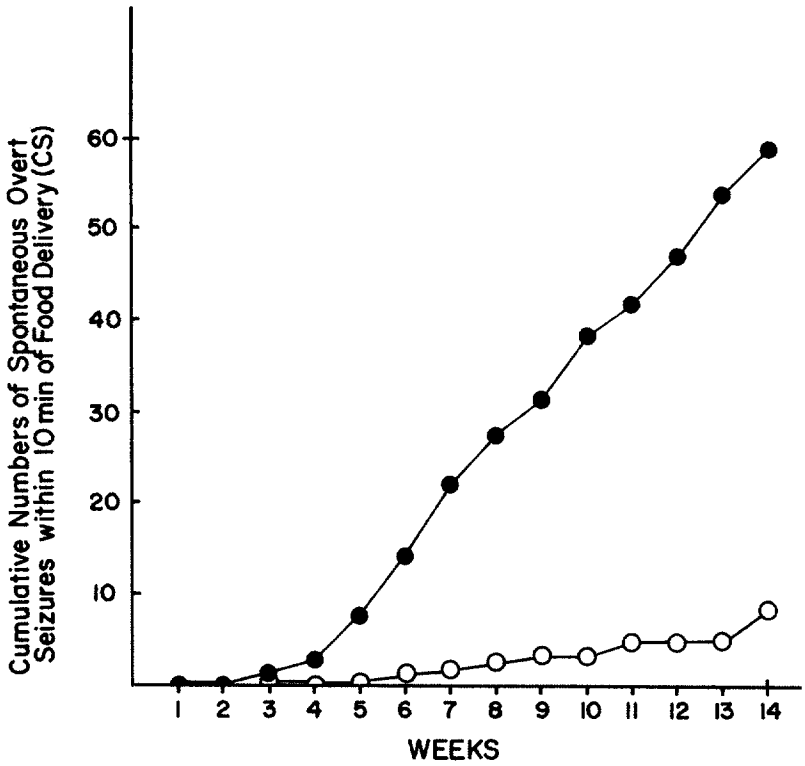

FIGURE 2 Cumulative numbers of paroxysmal, stereotyped behaviours displayed per daily 10 min observation period after the stimulus presentation over 14 successive weeks.

Copyright ©2001. All Rights Reserved.

the first one min interval. The distribution of the 8 overt displays by the reference group was randomly distributed over the 10 min observation period.

Figure 3 shows the results of Experiment III (two blocks of replicates combined) where the food stimulus was introduced into the cage (and the group) 10 min after the entry of the experimenter to the room and oral prednisolone was presented for two weeks, twice, during the experiment. As can be seen the numbers of overt seizures were visually reduced, as defined by the slope of the cumulative record approaching 0, during the consumption of the prednisolone. During the 10 min immediately after the experimenter entered the room and sat quietly (before presentation of food), there was a total of only 4 overt seizures during the 14 weeks of observation.

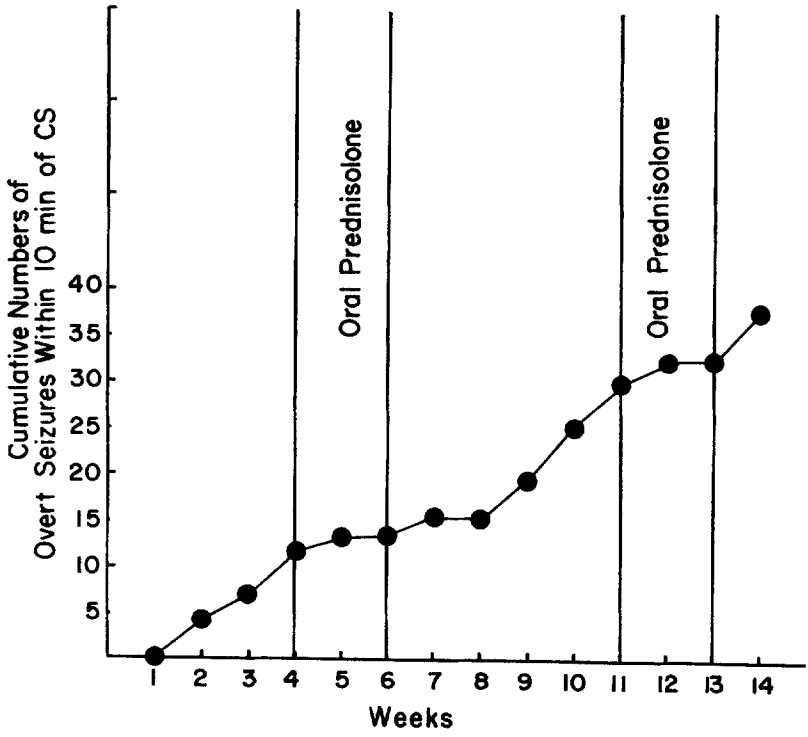

FIGURE 3 Cumulative numbers of "overt seizures" (paroxysmal, stereotyped behaviours) displayed within 10 min after the (food) stimulus presentation during conditions of normal tap water and 0.5 mg/cc of prednisolone in the water supply.

Copyright ©2001. All Rights Reserved.

On the other hand, the three rats (food available in hoppers *ad libitum*) that displayed evidence of conditioned seizures responded specifically to the sound of food dropping into the cage but not systematically to the sounds of either keys percussing or hands clapping. If an overt seizure began, it occurred within seconds of the presentation of the stimulus. As can be seen in Table I, the overt seizures occurred primarily following the presentations of the food sounds. The duration of these seizures were tens of seconds longer than those few instances where the shaking key sound was followed by seizures.

There were three potentially important qualitative observations. First, even though the food was available *ad libitum* through the food hoppers, the majority of rats ($n = 20$ to 30) in the rack began to eat the food cubes (same food as in hoppers) when they were presented (daily) through the top of the cage. Social facilitation was indicated by the escalating sound produced by dozens of rats gnawing simultaneously. Secondly, about 10% of the rats displayed periods of lethargy during which time they did not eat the food pellets for about three to four successive days. Third, there were two conspicuous patterns in the evolution of the overt seizures. The first type involved the initial display of headnods or sniffing and then the occurrence of the rearing, forelimb clonus and falling. The second type of pattern began with the rearing, rapid, forelimb clonus and falling but the latency on successive days became shorter and shorter. Specific examples are shown in Table II.

TABLE I Durations of overt seizures defined as rearing and rapid forelimb clonus during the two min following the presentation of sounds of food dropping into a wire cage (the putative conditioned stimulus), keys rattling, or hands clapping for three epileptic rats

Stimulus	*Rat* 1	*Rat* 2	*Rat* 3
Food	36	18	0
Clapping	0	0	0
Keys	9	12	0
Clapping	0	6	0
Food	67	21	43
Keys	0	0	5
Clapping	0	0	0
Food	14	6	17
Keys	0	0	0

Copyright ©2001. All Rights Reserved.

TABLE II Qualitative and quantitative shifts in overt behaviours for two rats over days during the 10 min period after the daily presentation of a (food) stimulus. HN (head nods); SN (rapid sniffing and searching); FPC (rearing, forepaw clonus and falling). Numbers refer to latency (in min) of the display of the behavior

Day	*Rat* 7207	*Rat* 7210
1	0	0
2	0	0
3	0	0
4	0	FPC (5.9 min)
5	HN (6.3 min)	FPC (0.5 min)
6	0	FPC (0.1 min)
7	SN (4.7 min)	
8	0	
9	HN (1.1 min)	
10	FPC (0.5 min)	
11	FPC (1.2 min)	

DISCUSSION

The results of this experiment support our other observations that synchronized feeding increases the daily occurrence of "spontaneous" paroxysmal stereotyped behaviours that are identical to those associated with verifiable, limbic electrical seizures. The behaviours were conspicuously abnormal and could not be confused with normal activity. The overt stereotyped behaviours were indiscriminable from the Racine Stages 4 and 5 overt displays that are routinely induced by brief (a few sec) daily electrical stimulation of the limbic system by implanted electrodes.

The primary role of conditioned or synchronized release of CRF in the display of these behaviours within one min of food (stimulus) presentation was supported by several specific results. First, in both of the major experiments, over half of all of the "overt seizures" occurred within the first min of the daily food presentation. One would expect major contributions from the release of ACTH or corticosterone to require at least five min unless neurons are sensitized to rates of change in the concentrations. Secondly, the display of these stereotyped sequences was suppressed during treatment by oral prednisolone which blocks glucocorticoid receptors and simulates the effects of lesioning the central nucleus of the amygdala.

Although the action of the secretion of CRF from the paraventricular nucleus upon the corticotropes of the anterior pituitary can

Copyright ©2001. All Rights Reserved.

release ACTH within seconds, the latency of onset of about 20% of the spontaneous seizures within seconds after entry into the room strongly suggested a faster neurochemical process. The time required to double ACTH levels within the blood in rodents is about 5 to 7 min. Although this could explain the second minor peak in seizure latencies within our observations, it would not be sufficient to explain the observation that about 20% of the seizures occurred almost immediately.

The argument that the paroxysmal stereotyped behaviours were conditioned is supported by the two to three week delay (Experiment II) in the display of these behaviours in the group studies. Although the counterargument that this time was required to synchronize the diurnal peak in CRF release (so that any stimulus would release this epileptogenic neuropeptide), is a valid, competitive explanation, it would not explain fully the result of Experiment III. In that study the experimenter entered the room 10 min before the presentation of the food yet most of the overt, paroxysmal stereotyped behaviours occurred after the food presentation. Both the latency of onset of the behaviours following the presentation of the putative conditioned stimulus and the time (over days) required for the "acquisition" of the behavior is consistent with a learning process.

However to verify this presumption, the optimal experiment would require the presentation of a completely neutral stimulus (such as tone), followed by repeated (daily) temporal contiguity of both the stimulus and synchronized food presentation, and then ultimately by the presentation of the "neutral stimulus" by itself. If the incidence rate of "overt seizures" then continued when the "neutral" stimulus was presented by itself (operationally, a conditioned stimulus) but did not continue when other stimuli were presented and the effectiveness of the putative conditioned stimulus decreased over trials after the pairing with food presentation was stopped, then the criteria for classical conditioning would be achieved. This condition was partially achieved by three rats (Tab. I) that, when tested in another setting, displayed the stereotypical motor seizures in response to the conditioned stimulus (sound of food dropping into a cage) 1 m away but did not respond systematically to either the sound of rattling keys or of hands clapping at comparable levels of intensity.

Our hypothesis is that over-stimulation of CRF-related systems within the amygdala-hippocampal formation is highly correlated with

Copyright ©2001. All Rights Reserved.

the processes that initiate the propagation of the seizures. Conditioned elevation of the activity of the CRF-ACTH-corticosterone system superimposed upon normal diurnal variations should also increase the probability that an overt seizure will be manifested. In the chronically epileptic rats, these stimuli included presentation of food cubes even though the rats were not food deprived. The degree to which the "information" within the continuous sounds of group eating and the social facilitation contributed to the seizures must be still be determined.

The possible confounding effects from an "acoustic startle" effect during the daily presentation of food was minimal. Only about 20% of the paroxysmal stereotyped behaviours occurred within seconds upon the quiet and slow entry to the test rooms. This confound is important in light of the role of the central amygdala in the generation of this reflex and the conspicuous "ear twitching" (which we have found moderately correlated with the amount of damage within the suprageniculate nucleus) that occurs in these epileptic rats. However if these results were completely artifacts of acoustic startle, the learning curves should not be apparent and the seizures would have occurred to any sudden noise, such as rattling keys. In addition, daily presentations of brief (1 sec), intermittent 1000 Hz, 70 db tones (for 10 min) to these rats have not provoked statistically significant increases in the "overt seizures" (Harrigan, unpublished studies).

In this particular model for complex partial seizures, the propagation to motor centers (and hence overt, obvious displays) is more likely because the major impedance to this generalization, the substantia nigra reticulata (Gale, 1988) is always damaged (Persinger *et al.*, 1993). We suspect that the same seizure processes that remain subclinical and contained within subcortical limbic structures of the highly gyrenencephalic brain of the human being (Persinger, 1994), are quickly propagated throughout the lissencephalic organization of the rat cerebrum and consequently become overtly conspicuous. This allows easier measurements and more direct inferences.

The theoretical and clinical implications of our experiments, if generalizable to human begins, are obvious. A significant number of patients who are diagnosed as partial complex epileptics also exhibit "pseudoseizures" or psychogenic seizures because of the absence of verifiable electroencephalographic anomalies (Savard and Andermann, 1993; Persinger, 1994) even though these electrical

Copyright ©2001. All Rights Reserved.

signatures would be restricted to *only* those paroxysmal discharges that propagate to the cerebral cortices and involve a critical number of cortical modules (Goldensohn, 1983; Persinger and Makarec, 1993).

The neuroprocesses or mechanisms by which complex partial patients exhibit both electrically verifiable seizures and "learned" displays has not been clear. The present model suggests that socially conditioned stimuli and contexts (*e.g.*, anticipation of anxiogenic situations, social settings) that are associated with a sudden increase in the activation of the CRF-ACTH system through the primary amygdaloid-paraventricular hypothalamic pathways may be centrally involved. If this hypothesis is valid then the psychological consequences of "psychogenic seizures" can be as significant to the patient as those associated with more traditional electroencephalographic patterns.

Approximately 20% of all epileptic patients do not exhibit complete suppression of their seizures by contemporary medications. About 80% of these patients exhibit partial complex epileptic (limbic) seizures with electrical foci within the amygdaloid-hippocampal regions (Heinemann, Zhang and Elder, 1993). The potential role of learning or conditioning in the display of psychogenic seizures by these patients may explain their complex responsiveness to some psychological interventions such as verbal instruction and the strong concordance with social stimuli. However learned or conditioned non-epileptic seizures do not necessarily imply conscious or volitional control or even malingering. The difference between EEG-verifiable seizures and psychogenic non-epileptic seizures may be analogous to the similarities operationally and neurogenically between the unconditioned stimulus and the conditioned stimulus.

References

Aldenhoff, J. B., Gruol, D. L., Rivier, J., Vale, W. & Siggins, G. R. (1983) Corticotrophin releasing factor decreases postburst hyperpolarization and excites hippocampal neurons. *Science*, **221**, 875–877.

Bedard, A. W. & Persinger, M. A. (1995) Prednisolone blocks extreme intermale social aggression in seizure-induced, brain-damaged rats: implications for the amygdaloid central nucleus, corticotrophin releasing factor and electrical seizures. *Psychological Reports*, **77**, 3–9.

Bureau, Y. R. J., Peredery, O. & Persinger, M. A. (1994) Concordance of quantitative damage within the diencephalon and telencephalon following systemic pilocarpine (380 mg/kg) or lithium (3 mEq/kg)/pilocarpine (30 mg/kg) induced seizures. *Brain Research*, **648**, 265–269.

Copyright ©2001. All Rights Reserved.

Curtis, A. L. & Valentino, R. J. (1994) Corticotrophin-releasing factor neurotransmission in locus ceruleus: a possible site of antidepressant action. *Brain Research Bulletin*, **35**, 581–587.

Dallman, M. F., Akana, S. F., Bradbury, M. J., Strack, A. M., Hanson, E. S. & Scribner, K. A. (1994) Regulation of the hypothalamo-pituitary-adrenal axis during stress, feedback, facilitation and feeding. *Seminars in the Neurosciences*, **6**, 205–213.

Desjardins, D. & Persinger, M. A. (1995) Strong quantitative associations between biting behavior and cellular density within the central nucleus in male rats with lithium/pilocarpine-induced seizures. *Perceptual and Motor Skills*, **81**, 635–641.

Gale, G. (1988) Progression and generalization of seizure discharge: anatomical and neurochemical substrates. *Epilepsia*, **19**, S15–S34.

Gates, J. R. & Erdahl, P. (1993) Classification of non-epileptic events. In: Rowan, A. J. and Gates, J. R. (Eds.). *Non-epileptic seizures*, Butterworth-Heinemann: Boston, pp. 21–30.

Goldensohn, E. S. (1983) Symptomatology of nonconvulsive seizures: ictal and postictal. *Epilepsia*, **24**, S5–S21.

Haas, D. A. & George, S. R. (1988) Single and repeated mild stress increases synthesis and release of hypothalamic corticotrophin-releasing factor. *Brain Research*, **416**, 230–237.

Harrigan, T., Peredery, O. & Persinger, M. A. (1991) Radial maze learning deficits and mediodorsal damage in context of multifocal, seizure-induced brain lesions. *Behavioral Neuroscience*, **105**, 482–486.

Heinemann, U., Zhang, C. & Edler, C., Entorhinal cortex-hippocampal interactions in normal and epileptic temporal lobe. *Hippocampus*, **3**, 89–98.

Honchar, M. P., Olney, J. W. & Sherman, W. R. (1983) Systemic cholinergic agents induce seizures and brain damage in lithium-treated rats. *Science*, **220**, 323–325.

Ixart, G., Siaud, P., Barbanel, G., Mekaouche, M., Givalois, L. & Assenmacher, I. (1993) Circadian variations in the amplitude of corticotrophin-releasing hormone 41 (CRH 41) episodic release measured *in vivo* in male rats: correlations with diurnal fluctuations in hypothalamic and median eminence CRH41 contents. *Journal of Biology Rhythms*, **8**, 297–309.

Koob, G. F., Heinrichs, S. C., Menzaghi, F., Pich, E. M. & Britton, T. (1994) Corticotrophin releasing factor, stress and behavior. *Seminars in the Neurosciences*, **6**, 221–299.

LeDoux, J. E. (1994) The amygdala: contributions to fear and stress. *Seminars in the Neurosciences*, **6**, 231–247.

Liang, K., Melia, K. R., Campeau, S., Falls, W. A., Miserendino, M. J. D. & Davis, M. (1992) Lesions of the central nucleus of the amygdala but not the paraventricular nucleus of the hypothalamus block the excitatory effects of corticotrophin releasing factor on the acoustic startle reflex. *Journal of Neuroscience*, **12**, 2313–2320.

Mistleberger, R. E. & Rusak, B. (1988) Food-anticipatory circadian rhythms in rats with paraventricular and lateral hypothalamic ablations. *Journal of Biological Rhythms*, **3**, 277–291.

Mulder, O. G. (1990) Management of Pseudo-epileptic seizures. In: Dam, M. and Gram, L. (Eds). *Comprehensive Epileptology*: Raven. N.Y., pp. 495–504.

Persinger, M. A. (1994) Seizure suggestibility may not be an exclusive differential indicator between psychogenic and partial complex seizures: the presence of a third factor. *Seizure*, **3**, 215–219.

Persinger, M. A. (1995) Geophysical variables and behavior. LXXIX. Overt limbic seizures are associated with concurrent and premidscotophase geomagnetic activity: synchronization by prenocturnal feeding. *Perceptual and Motor Skills*, **81**, 83–93.

Persinger, M. A. & Makarec, K. (1993) Complex partial epileptic signs as a continuum from normals to epileptics: normative data and clinical populations. *Journal of Clinical Psychology*, **49**, 33–45.

Persinger, M. A., Makarec, K. & Bradley, J.-C. (1988) Characteristics of limbic seizures evoked by peripheral injections of lithium and pilocarpine. *Physiology and Behavior*, **44**, 27–37.

Copyright ©2001. All Rights Reserved.

Persinger, M. A., Bureau, Y. R., Kostakos, M., Peredery, O. & Falter, H. (1993) Behaviours of rats with insidious brain damage induced by seizures following single peripheral injections of lithium and pilocarpine. *Physiology and Behavior*, **53**, 849–866.

Porter, R. J. (1993) Epileptic and non-epileptic seizures. In: Rowan, A. J. and Gates, J. R. (Eds.). *Non-epileptic seizures*. Butterworth-Heinemann: Boston, pp. 9–20.

Ramsey, R. E., Cohen, A. & Brown, M. C. (1993) Coexisting epilepsy and non-epileptic seizures. In: Rowan, A. J. and Gates, J. R. (Eds.). *Non-epileptic seizures*. Butterworth-Heinemann: Boston, pp. 47–54.

Racine, R. J. (1972) Modification of seizure activity by electrical stimulation: II. Motor seizure. *Electroencephalography and Clinical Neurophysiology*, **32**, 281–294.

Savard, G. and Andermann, F. (1993) Non-epileptic seizures: the interface between neurologic and psychiatric events. In: *Non-epileptic seizures* (Eds. Rowan, A. J. and Gates, J. R.). Boston, Butterworth, pp. 193–201.

Weiss, J. M., Stout, J. C., Aaron, M. F., Quan, N., Owens, M. J., Butler, P. D. & Nemeroff, C. B. (1994) Depression and anxiety: role of the locus coeruleus and corticotrophin-releasing factor. *Brain Research Bulletin*, **35**, 561–572.

Copyright ©2001. All Rights Reserved.